YEAST AND HUMAN MUTATOR GENES AND THEIR RELATIONSHIP TO INHERITED CANCER SUSCEPTIBILITY. R. Kolodner*, Dana-Farber Cancer Institute, Harvard Medical School, 44 Binney Street, Boston, MA 02115.

Much of our understanding of mismatch repair comes from genetic and biochemical analysis of the mechanism of gene conversion and the origin of spontaneous mutations. The best studied mismatch repair system is the *E. coli* MutHLS system. This system requires 3 specialized proteins, MutS which recognizes mispaired bases, MutH which nicks the unmethylated daughter strand produced by DNA replication and MutL which coordinates the activities of MutS and MutH. The yeast *S. cerevisiae* contains 5 MutS and 3 MutL homologues of which 1 MutS homologue, MSH2, and 2 MutL homologues, PMS1 and MLH1, function in the major mismatch repair pathway. Analysis of MSH2, PMS1 and MLH1 has indicated they function in post replication repair and genetic recombination; mutations in these genes result in a high spontaneous mutation rate, instability of dinucleotide repeat sequences, altered gene conversion and loss of gene conversion polarity gradients consistent with defects in mismatch repair. Biochemical analysis of these proteins has shown that MSH2 recognizes mispaired bases in DNA and that PMS1 and MLH1 form a complex which binds to MSH2 bound to a mispaired base.

Hereditary non-polyposis colon cancer (HNPCC) is the major form of familial colon cancer thought to account for up to 5 to 15% of colon cancer and HNPCC is also associated with other types of cancer. It is thought that up to 60% of HNPCC maps to a locus on human chromosome 2p and 30% maps to a locus on chromosome 3p. Tumors from HNPCC patients as well as variable proportion of a large variety of different sporadic tumors are associated with instability of simple DNA repeat sequences. This instability is similar to that observed in mismatch repair deficient mutants of *E. coli* and *S. cerevisiae* and suggested that HNPCC might be due to an inherited mismatch repair defect. To test this, the human homologues of the MSH2 and MLH1 genes were cloned using the same degenerate PCR methods used to identify the *S. cerevisiae* genes. The chromosomal locus encoding each gene was cloned and the entire intron-exon structure was determined. The hMSH2 gene was found to be encoded by 16 exons and map to chromosome 2p21 near the chromosome 2 HNPCC locus. Analysis of a number chromosome 2-linked HNPCC family has demonstrated nonsense, frame shift and missense mutations which co-segregate with HNPCC in different families. The hMLH1 gene was found to be encoded by 19 exons and map to chromosome 3p21-23 near the chromosome 3 HNPCC locus. Analysis of chromosome 3-linked HNPCC families has demonstrated frame shift and missense mutations which co-segregate with HNPCC in different families. These data provide strong evidence that HNPCC is caused by inherited defects in mismatch repair that lead to a high spontaneous mutation rate in cells that then progress to become tumor cells. The hMSH2 and hMLH1 genes appear to be the first members of a new class of cancer susceptibility genes.

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